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GELLAN-BASED SYSTEMS FOR SUSTAINED OPHTHALMIC DELIVERY OF OFLOXACIN.

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ABSTRACT

It is common knowledge that the ocular bioavailability and therapeutic response of drugs applied topically as eye drops is very poor, this is due to rapid precorneal drainage of the instilled dose, which could be overcome by the use of *in-situ* gelling systems that undergo a sol-gel transition in the cul-de-sac. This work describes the ophthalmic formulation of an antibacterial agent ofloxacin, based on the concept of ion-activated *in-situ* gelation by using the polymer Gellan gum, a novel vehicle for sol-gel transition, which gels in the presence of mono/divalent cations present in the tear fluid. The formulations were characterized for *in vitro* drug release and rheological properties. The physical stability and interaction between the exipients of the selected formulations were determined following steam sterilization and storage at 25ºC and 40ºC. The optimized formulations were therapeutically efficacious and demonstrate to possess consistency that is favorable to prolong the drug release properties over an extended period of time (12 h). The physical stability, following steam sterilization and storage, the optimum viscosity combined with sustained release of the drug make the formulations "C" and "C-Beta" the promising formulations as an alternative to conventional eye drops.

KEYWORDS: Gelrite®, ofloxacin, *in-situ* gelation, sustained release.

INTRODUCTION

Topical application of antibacterial therapy to the conjunctival sac is usually an effective avenue for treating bacterial conjunctivitis. A very common disadvantage of using eye drops is a rapid elimination of the solutions containing drug and their poor bioavailability. The rapid elimination has different causes: the amount and the structure of the tear film present, the capacity of lower eyelid sac and the different defense mechanisms of the eye against foreign matter (Ooteghem, 1993). The poor bioavailability of eye drops is due to the short precorneal residence time (Cohen *et al*., 1997). The conventional therapy of bacterial conjunctivitis requires frequent administration of eye drops at an interval of 2-4 hours, which results in patient compliance problem. In addition to it the frequent administration of high concentration of drug in the eye leads to systemic side effects. To increase ocular bioavailability and duration of drug action, various ophthalmic vehicles such as viscous solutions, gels, ointments or polymeric inserts have been used (Mitra, 1993). Although the corneal contact time has been increased by these vehicles but they have not been widely accepted because of blurred vision (in the case of ointments) and lack of patient compliance (in the case of inserts). From the point of view of patient acceptability, a liquid dosage form that can sustained drug release and remain in contact with the cornea of eye for extended periods of time is ideal. Such delivery system consists of phase transition polymers that are instilled in the liquid forms and shifts to the gel phase once in the cul-de-sac of the eye. Three methods have been employed to cause phase transition on the eye surface: change in pH, change in temperature and ion-activation. The polymers mostly used in the *in-situ* gelling systems are *viz.* sodium alginate (Cohen *et al*., 1997), Carbopol® and methyl cellulose (Kumar *et al*., 1994),

cellulose acetate phthalate latex (Gurney *et al*., 1985), poloxamer-407 (Miller and Donovan, 1982) and Gelrite® (Sultana *et al.*, 2004) *etc*. Gelrite® is a gellan gum that is a high molecular mass, linear anionic heteropolysaccharide produced aerobically from the bacterium *Auromonas (pseudomonas) elodea*, renamed *Sphingomonas paucimobilis*. The polymer backbone is comprised of a tetrasaccharide repeat unit of glucose, glucuronic acid and rhamnose in the molar ratio 2:1:1. It has a characteristic property of temperature dependent and cation-induced gelation. The gelation involves the formation of an ordered state of gellan chains. X-ray diffraction studies have confirmed that a double helix of gellan chains is formed by complexation with cations and hydrogen bonding with water (Sanzgiri *et al.*, 1993).

Ofloxacin is a second-generation flouroquinolone derivative used to treat bacterial infections in the eye especially conjunctivitis caused by Gram negative bacteria. It affects bacterial DNA- *gyrase* without affecting mammalian DNA activity. The topical ophthalmic dose of ofloxacin is 2-3 drops of a 0.3% (w/v) solution in the affected eye(s) every 4 hour or at every hour in case of severe infection (Reynolds, 1989). The main aim of the present work was to develop an ion-activated *in-situ* gelling ocular formulation of ofloxacin. Gelrite® was used as vehicle for the development of the formulation that could provide sustained release of the drug for 12 hours.

MATERIALS AND METHODS

Materials

Ofloxacin (Courtsey, Cadila, Ahmedabad, India), Gelrite® (Courtsey, Kelco division of Merck, USA), Propyl paraben, Methyl paraben and β-Cyclodextrin (S.D. fine. Chem. Ltd, Mumbai, India), Tris maleate buffer (Scientific Delhi, India). Other formulation excipients were pharmaceutical grade and obtained from standard commercial suppliers.

Preparation of formulation

(A) Preparation of in-situ gelling system containing free drug

The polymer solutions were prepared by dispersing the polymer (0.3, 0.4, 0.5, 0.6, and 0.7 g) in Tris maleate buffer at pH 6.0 and stirring at 35°C for 24 hours. 0.27%, (w/v) of ofloxacin was added to it and mixed. The preservatives propyl paraben 0.01% and methyl paraben 0.05% were added to it and the formulations were made up to volume with Tris maleate buffer at pH 6.0 (Table 1).

(B) Preparation of in-situ gelling system containing complexed drug

Preparation of drug and β-Cyclodextrin complex:

The solid inclusion complexes of ofloxacin and β-Cyclodextrin were prepared by freeze-drying. The drug and the polymer were dissolved separately in 25% aqueous ammonia solution. The molar mixture (1:1) was stirred at 30°C at room temperature for 24 hours and then freeze dried for 24 hours. The freeze-dried product was then sieved through 180 micromesh to give the final product. The inclusion complex containing drug, was added to the optimized formulation containing Gelrite® 0.5% , propyl paraben 0.01%, methyl paraben 0.05% in Tris maleate buffer of pH 6.0 (The formulation was optimized on the basis of in-vitro release studies).The formulations were packaged in amber coloured glass vials, capped with rubber bungs and sealed with aluminum caps. The formulations in their final pack were subjected to terminal sterilization by autoclaving at 121°C and 15 psig for 20 min.

Evaluation of Formulation

The prepared formulations were evaluated for the in-vitro release studies and drug content was analyzed by UV spectrophtometry at 288 nm (Double beam UV spectrphotometer, Hitachi-110, Japan), viscosity studies (by Cone and Plate Viscometer, Physica Rheolab, Australia), clarity by visual observation against a black and white background in a well-lit cabinet, Osmolarity was determined by osmometer (Fiske Associates USA), refractive index was checked by Abbe's Refractrometer (Scientific India), pH (Hanna Instruments), antimicrobial studies to

find out the sustained release of the drug from the prepared formulations, interaction studies and of course the stability study by HPTLC method.

In-Vitro Release Studies

The in-vitro release of ofloxacin from the formulations was studied by flow through apparatus fabricated in laboratory (Ali and Sharma, 1992). The dissolution medium was Simulated Tear Fluid (STF) of pH 7.4. The in-situ gel forming system was converted to gel upon addition of STF to it. The gel containing 2.7 mg of the drug was added to the jacketed flow through cell. 125 ml of the STF of pH 7.4 was placed in the flask and 1ml sample was withdrawn at regular intervals and replaced with fresh buffer (STF). The buffer was allowed to flow through the artificial eye of the flow through apparatus by using the peristaltic pump. The flow was regulated with flow regulator to 10 drops per minute (~0.4 ml per min.). To compensate blinking of the eye, air bubbles were blown in the artificial eye through an aerator. The content of the flask was continuously stirred with the help of a magnetic stirrer. The whole assembly was maintained at 37±0.5°C by the circulation of warm water through the jacket. The water from the water bath maintained at 37±0.5°C was circulated through the flow through cell and then through flask and finally to the sink. The aliquots were diluted with STF and analyzed by UV spectrophotometer at λ_{max} 288 nm.

Rheological Studies

The viscosities of the solution and the gel formed were determined by cone and plate viscometer using MK-22 spindle. For viscosity determination, 1ml of the sample was placed on the plate and spindle was touched with the sample, temperature was adjusted to 25°C and system was started. Data were obtained and the graphs were plotted between shear stress and shear rate of the formulations.

Antimicrobial Efficacy Studies

The microbiological studies were carried out to ascertain the biological activity of ophthalmic sol-to-gel system against microorganisms. This was done by agar diffusion test method employing cup-plate technique. Marketed eye drops (Standard solutions) of the drug and the developed formulations containing free and complexed drug (Test solutions) were poured into cups made by sterile borer into sterile nutrient agar previously seeded with test organisms (S. aureus, P. aeruginosa, E. coli). After allowing diffusion of the solutions for 2 hours the agar plates were incubated at 37°C for 24 hours. The zone of inhibition (ZOI) in mm measured around each cup was compared with that of control. The entire operation except the incubation was carried out in a laminar flow unit. Each solution was tested in triplicate. Both positive and negative controls were maintained throughout the study.

Interaction Studies

Interaction studies were done in order to investigate any interaction between drug and excipients and to study the effect of sterilization. The interaction studies were conducted by UV, FTIR and DSC methods.

UV Scanning

Ophthalmic gel before and after sterilization were dissolved in STF at pH 7.4. The solutions were filtered through Whatman filter paper no.42 and solutions were scanned. UV spectrophotographs recorded were taken as quantitative in order to assess the changes in peaks, pattern of curves etc.

FTIR Studies

FTIR spectra of ophthalmic gel were compared with the spectra of pure drug. Spectra of drug and polymer were taken and analyzed for any major interaction. These were done qualitatively in order to assess the pattern of peaks and for comparison purpose. The FTIR spectra of the polymer and drug with polymer, β-Cyclodextrin and drug with β-Cyclodextrin were taken also.

DSC Studies

DSC of the samples was performed using DUPONT model 910 (USA) systems. DSC of pure drug, polymer and polymer drug mixture were done for ophthalmic formulations. DSC of β-Cyclodextrin and mixture of β-Cyclodextrin with drug were taken for the ophthalmic gel. The samples were taken in solid state in the pan and were compressed with high-pressure press. All the samples (5 mg each) were treated at inert nitrogen atmosphere by oxidation method at the heat rate 10°C/min, flow of gas 35 cc/min and temperature range 50-350°C.

Stability Studies

Stability studies were carried out as per ICH guidelines. The drug content in the package was analyzed by HPTLC (Srividya *et al*., 2003). Standard curve of ofloxacin was prepared using methanolic solution of ofloxacin in concentration range of 300-1000 ng/mL. Peak area versus drug concentration was treated by linear least square regression analysis.

Standard curve of ofloxacin by HPTLC

The n-butanol: methanol: strong ammonia: water (4:1:0.9:1.3) system gave the most compact spots as well as separated the degraded products from the pure drug, this system was chosen as the mobile phase. The optimized formulation was then kept at condition of 75±5% relative humidity. Whole assembly was kept inside a hot air oven at temperature 40± 2°C for 90 days and samples were again analyzed after storage for any degradation.

RESULTS AND DISCUSSION

Selection of formulation ingredients

Buffers play a pivotal role in formulating ophthalmic drops. They contribute significantly to chemical stability and clinical response and also influence the comfort and safety of the product hence the importance of selecting a suitable buffer, which ensures product stability and desired drug solubility. The studies in various buffer solution indicate that the drug is soluble in 0.01M Tris maleate buffer of pH 6.0 at the dosage level desired (0.27%, w/v). The solutions were stable at elevated temperature and autoclaving.

The marketed eye drops were found a pH of 6.2. It has been reported that the ocular penetration of levofloxacin, the (-) isomer of ofloxacin is maximum at around pH 6.5.Tris maleate buffer; pH 6.0 was therefore selected as the vehicle for the formulated eye drops.

Table 1: Formulae of the sol to gel systems containing free drug and complexed drug

S. No.	Ingredients	Amount (g)					
		A	B	C	D	E	C-Beta
1	Ofloxacin	0.270	0.270	0.270	0.270	0.270	-----
2	Gelrite®	0.30	0.40	0.50	0.60	0.70	0.50
3	Propyl paraben	0.01	0.01	0.01	0.01	0.01	0.01
4	Methyl paraben	0.05	0.05	0.05	0.05	0.05	0.05
5	Tris maleate Buffer pH 6.0 (ml)	100	100	100	100	100	100
6	Complexed (Ofloxacin β-Cyclodextrin)	—	—	—	—	—	1.243 g equivalent to 0.270 g of drug

Gelrite® is a polysaccharide low acetyl gellan gum, which form clear gel in the presence of mono/divalent cations (Rozier et al., 1989). The pH of aqueous solution of Gelrite® is neutral. Propyl paraben and methyl paraben were used as preservative in the concentrations 0.01 % (w/v) and 0.05 % (w/v) respectively.

Preparation of Formulations

The two main prerequisites of an in-situ gelling system are viscosity and gelling capacity. The formulation should have an optimum viscosity that will allow easy instillation into the eye as a liquid (drops) which would undergo a rapid sol-to-gel transition triggered by the presence of cation in the tear fluid. Additionally the gel formed in-situ should preserve its integrity without dissolving or eroding for a prolonged period of time. Table1 shows the formulae of sol-to-gel system containing free drug and in situ gelling system containing complexed drug. The contribution of each ingredient to the osmotic pressure of the formulation was calculated in the concentration used in the terms equivalent to sodium chloride. Since the ingredients themselves contributed to the tonicity, no tonicity adjusting agents were added.

Evaluation of Formulation

The drug content was analyzed by UV spectrophtometry at 288 nm (Double beam UV spectrphotometer, Hitachi-110, Japan), clarity by visual observation against a black and white background in a well-lit cabinet, viscosity studies (by Cone and Plate Viscometer, Physica Rheolab, Australia). Osmolarity by osmometer (Fiske Associates USA), refractive index with Abbe's Refractrometer (Scientific India), and pH was determined by Hanna Instruments. And all of these physicochemical parameters of the formulations were found to be satisfactory as shown in Table 2. And both the optimized formulations were evaluated for the same parameters as mentioned above, after storage and the results were found to be satisfactory as shown in Table 3.

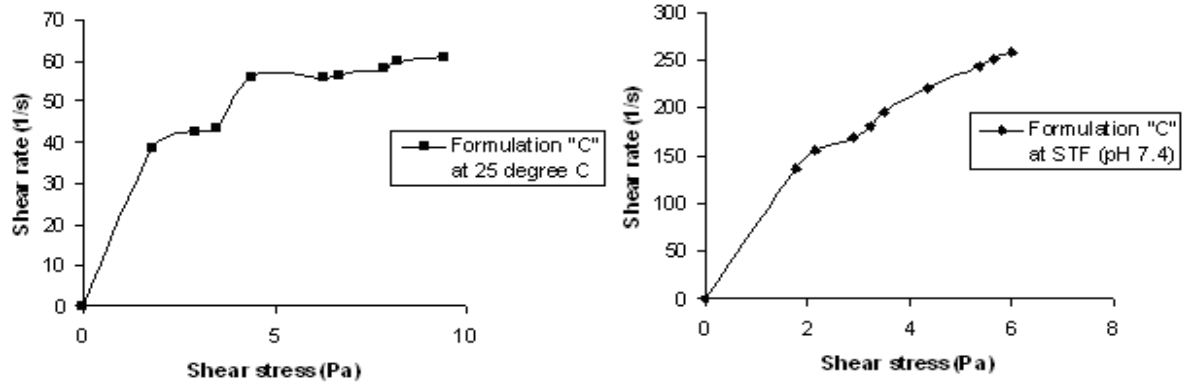
Table 2: Evaluation of Formulations

Formulations	Clarity	Drug content (%, w/v)	pH	Ref. Index	Osmolarity (mosmol)	Surface Tension (mN/m)	Viscosity (cps) sol
"C"	Clear solution	98	6.5	1.352	317	39	14800
"C-Beta"	Clear solution	97	6.5	1.361	324	38	13700
Marketed preparation.	Clear solution	100	6.2	1.4	319	42	-------

The formulations were liquid at room temperature and it underwent rapid transition into the gel phase upon contact with the cations present in simulated tear fluid (STF) of pH 7.4. Terminal sterilization by autoclaving had no effect on the pH, gelling capacity and viscosity of the polymer Gelrite®. Gelrite® is only polymer, which is capable of standing high temperature of autoclaving without loss of its functional properties and transparency.

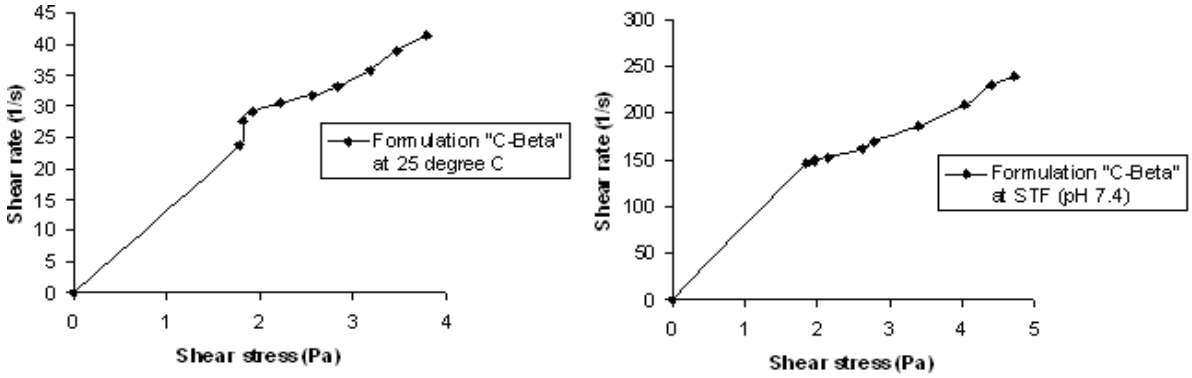
Rheological Studies

The viscosity studies were done and the formulations "C' and "C-Beta" were selected as optimized formulations for further studies, as they posses optimum viscosity. The formulations exhibited pseudoplastic rheology, as evidenced by shear thinning and an increase in the shear stress with increased angular velocity that can be observed in the Figures 1, 2 and 3. The viscosity was directly dependent on the polymeric content. No change in the viscosity of the formulations was observed after autoclaving. The desirable conversion of sol to gel was obtained on addition of STF (pH 7.4). It was supported by viscosity studies as shown in Figures 1, 2 and 3. The administration of ophthalmic preparations should influence as little as possible the pseudo-plastic character of the pre-corneal film (Ooteghem, 1993). Since the ocular shear rate is very high, ranging from 0.03 s^{-1} during inter-blinking periods to 4250–28500 s^{-1} during blinking (Bothner et al., 1990), viscoelastic fluids with a viscosity that is high under the low shear rate conditions and low under the high shear rate conditions are preferred for ophthalmic drug delivery.



(a) (b)

Fig. 1 Rheogram of formulation “C” at 25 ºC (a) and with STF at 37 ºC (b)



(a) (b)

Fig. 2 Rheogram of formulation “C-Beta” at 25 ºC (a) and with STF at 37 ºC (b)

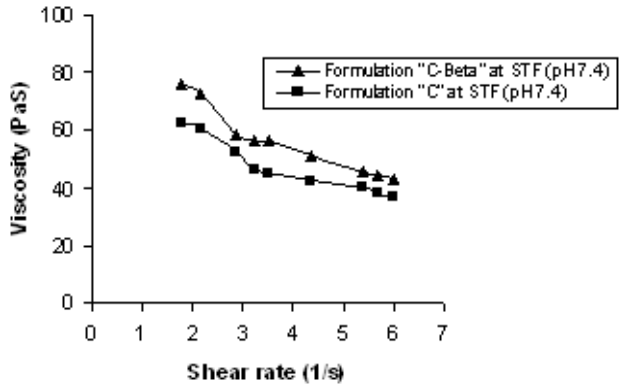


Fig. 3 Effect of shear rate on viscosity of the formulation “C” and “C-Beta” with STF at 37 ºC

Antimicrobial Efficacy Study

This study indicated that ofloxacin retained its antimicrobial efficacy in both the optimized formulations as shown in Fig. 4 and the formulations showed controlled release of the drug for 24 hrs.

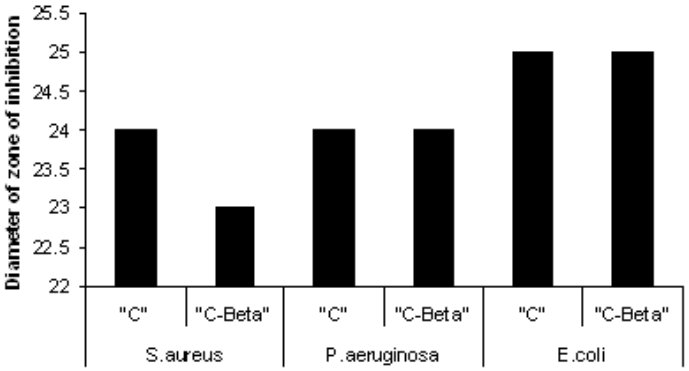


Fig. 4 Zone of inhibition (mm) by the formulations "C" and "C-Beta".

In vitro Drug Release Studies

In-vitro drug release conditions were simulated to those, which are likely to be encountered in the eye.The cumulative percent of ofloxacin release from the free drug and complexed drug are shown in Fig. 5, complexation with β-Cyclodextrin alter the release profile of ofloxacin from in-situ gelling system. The results clearly showed that the gels have the ability to retain Ofloxacin in its matrix network and that the premature drug release will not occur.

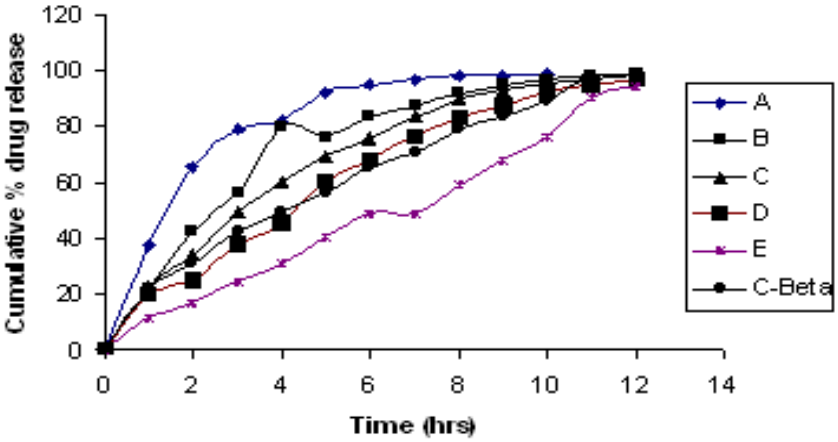


Fig. 5 Release profiles of ofloxacin from sol to gels A, B, C, D, E and C-Beta each point represent the mean ± S.D, n = 3

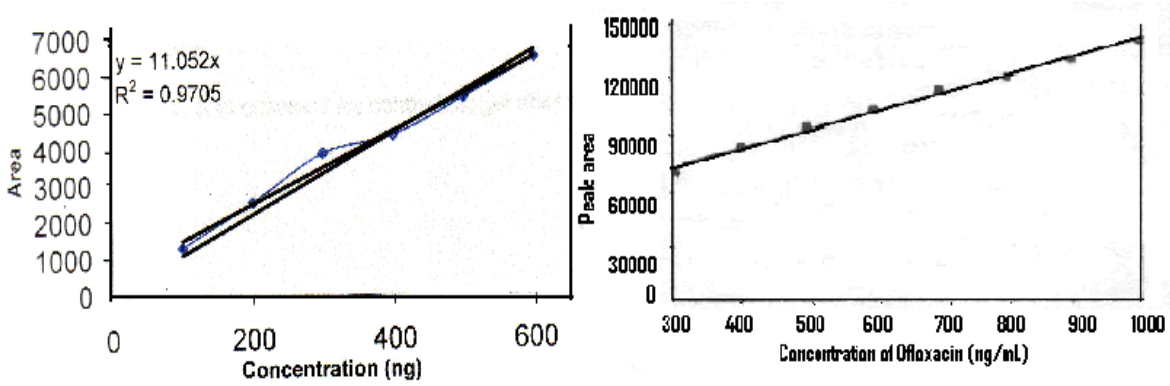
To study the drug release mechanism, the release data were fitted to the general exponential function: $M_t/M_0 = kt^n$ where M_0 is the initial amount of drug (amount of drug released at time zero) and M_t is the amount of drug released at time t, n is a diffusion exponent characteristic of the release mechanism, and k denotes the properties of the polymer and the drug (Martin, 1993). According to Brazel and Peppas, 2000, this equation has been frequently used in the literature owing to its utility in describing the relative importance of Fickian (n = 0.5) and non-Fickian,

anomalous diffusion (n = 1.0). If the exponent n is 0.5, the drug release is represented by a square root equation; if n = 1, the fraction release is zero order. Values of n greater than 0.5 indicate anomalous diffusion, generally due to the swelling of the system in the solvent before the release takes place.

However, in vitro drug release conditions are completely different from those occurred in eyes, but the results showed that "C" and "C-Beta" had the ability to retain the drug for 12 hrs.

Stability Studies

Stability studies by HPTLC showed that degradation product has Rf value of 0.43 and regressed value is found to be 0.98222 with Sdv is equal to 8.23. No interference was found from the excipient present in formulation. Thus, HPTLC method indicates stability of the packed product shown in Fig. 6.



(a) (b)

Fig. 6 Calibration curve (a) Stability Study curve by HPTLC (b)

Table3: Comparison of physical characteristics of ophthalmic gels "C" and "C –Beta" after storage

S. No	PHYSICAL CHARACTERISTICS										
	Formulations	Clarity		pH		Refractive index		Surface tension (mN/m)		Osmolarity (mosmol)	
		Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final
1	C	Clear solution		6.5	6.5	1.352	1.351	39	39	310	310
2	C-Beta	Clear solution		6.5	6.5	1.361	1.362	38	38	317	317

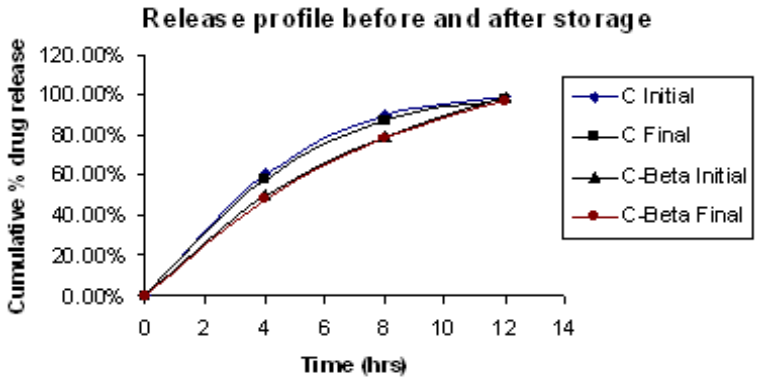


Fig. 7 Release of drug in formulations "C", "C-Beta" before and after storage

Cumulative release of drug from both the optimized formulations before and after storage were performed as shown in Fig. 7 and it was observed that there were no change in the amount of drug released for 12 hrs.

Interaction Studies on ophthalmic gels

Interaction studies were done in order to investigate any interaction between drug and polymer as well as to study the effect of sterilization.

UV Scanning

Ophthalmic gels before and after sterilization was dissolved in STF at pH 7.4. The solutions were filtered through Whatman filter paper no.42 and solutions were scanned. UV spectrophotographs recorded were taken as qualitative in order to assess the changes in peaks, pattern of curves etc and it was found that there were no changes in the peak patterns.

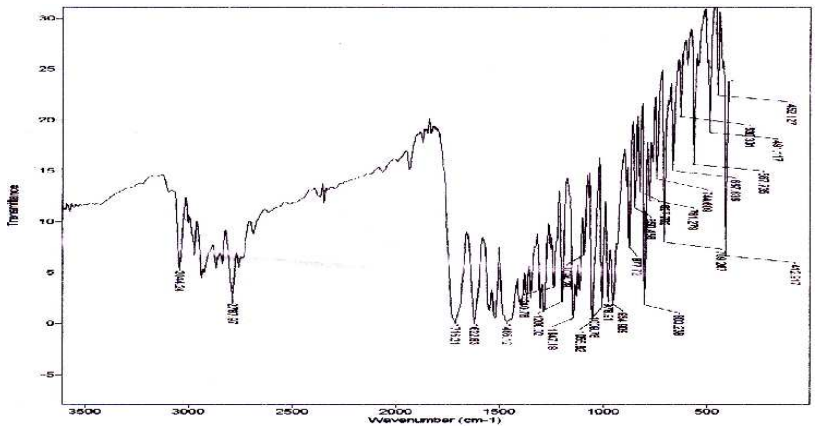


Fig. 8a FTIR of ofloxacin

IR Studies

IR spectra of ophthalmic gel were compared with IR spectra of pure drug. IR spectra of drug and polymer is taken and analyzed for any major interaction. These were done qualitatively in order to assess the pattern of peaks and for comparison purpose. The IR spectra of the drug (Fig. 8a), polymer (Fig. 8b) and drug with polymer (Fig. 8c)

are taken. The IR spectra of the β-Cyclodextrin (Fig. 8d) and drug complexed with β-Cyclodextrin (Fig. 8e) are also taken.

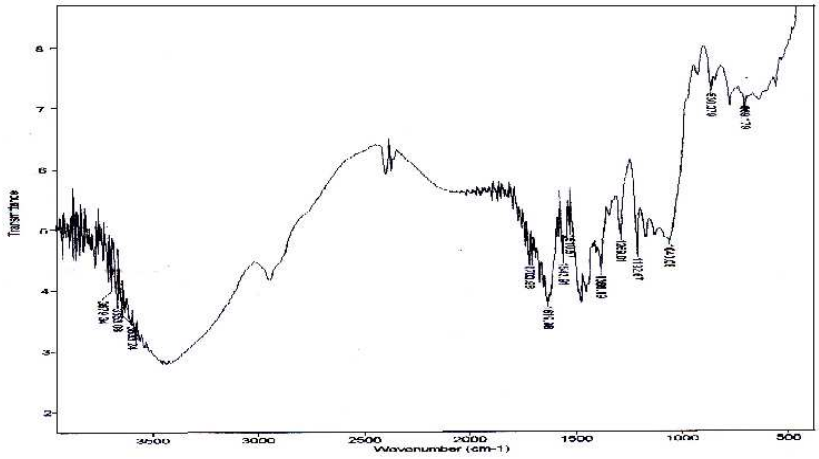


Fig. 8b FTIR of polymer Gelrite

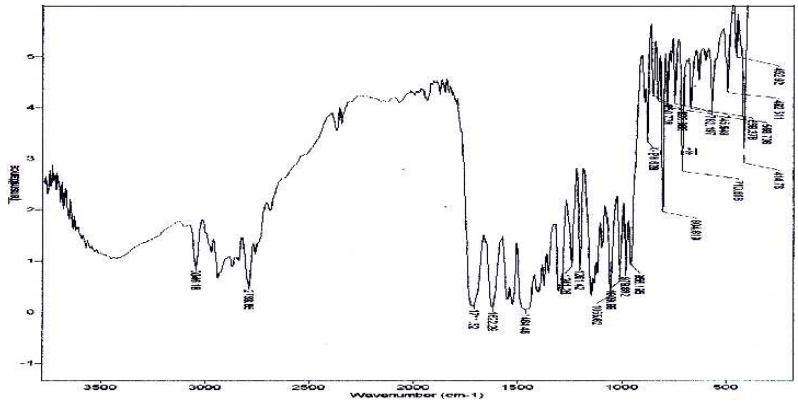


Fig. 8c FTIR of drug with polymer

The pattern of peaks of drug (Fig. 8a) and drug with the polymer (Fig. 8c) are almost same and they differs from that of peaks obtained due to polymer alone (Fig. 8b), this showed that there were no any interactions between drug and polymer present in formulation "C".

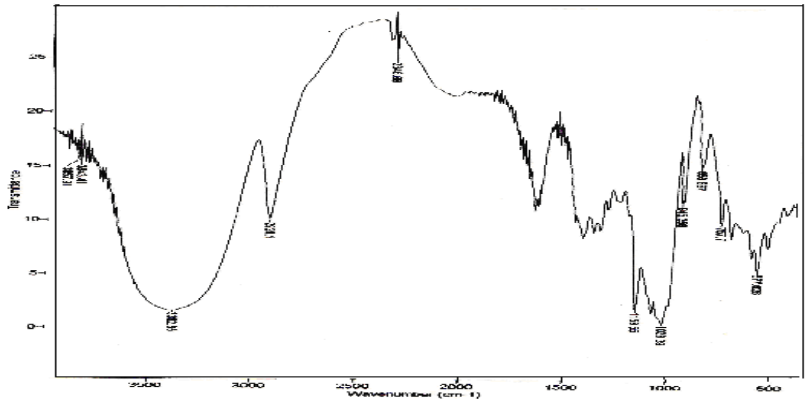


Fig. 8d FTIR of β-Cyclodextrin

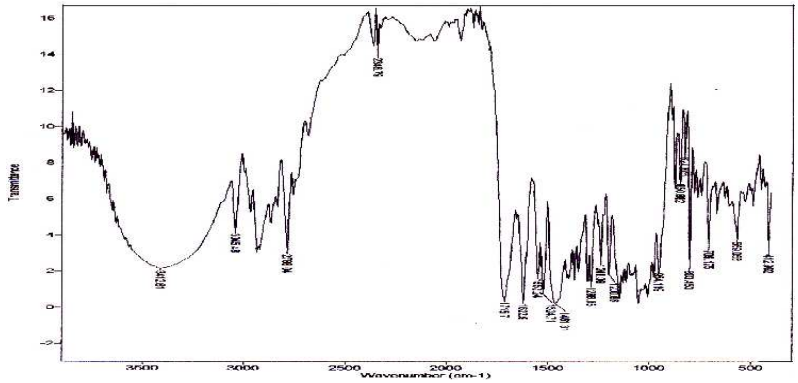


Fig. 8e FTIR of drug complexed with β-Cyclodextrin

The pattern of peaks of drug (Fig. 8a) are same as those of drug complexed with β-Cyclodextrin (Fig. 8e) and they differs from that of peaks obtained by β-Cyclodextrin alone (Fig. 8d), this indicated that there were no any interactions between drug and β-Cyclodextrin present in formulation "C-Beta".

DSC Studies

DSC endotherms of pure drug (Fig. 9), polymer (Fig. 10a) and polymer with drug (Fig. 10b) were done for ophthalmic formulations. DSC endotherms of β-Cyclodextrin (Fig. 11a) and β-Cyclodextrin complexed with drug (Fig. 11b) was taken for the ophthalmic gel. The samples were taken in solid state in the pan and were compressed with high-pressure press. DSC of the samples was performed using DUPONT model 910 (USA) systems. All the samples (5 mg each) were treated at inert nitrogen atmosphere by oxidation method at the heat rate 10°C/min, flow of gas 35 cc/min and temperature range 50-350°C.

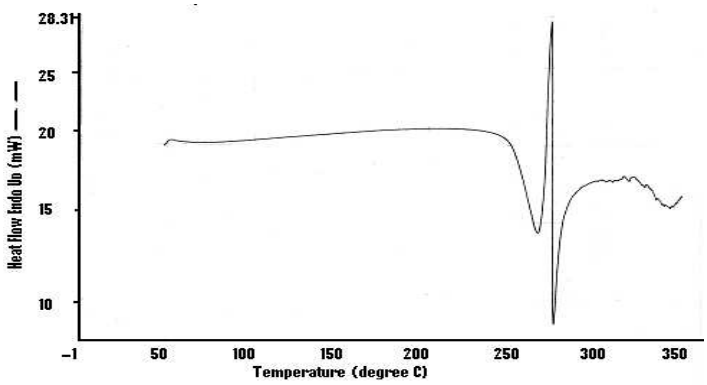


Fig. 9 DSC endotherm of drug (ofloxacin)

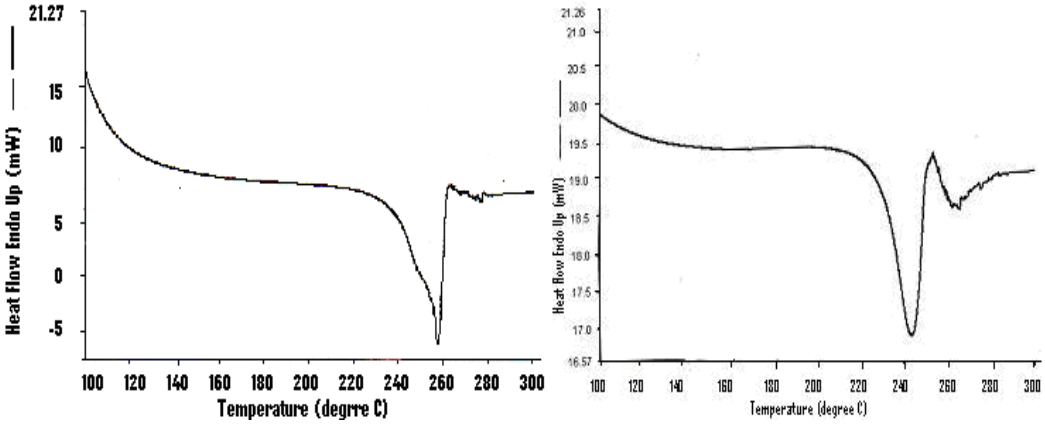


Fig. 10 DSC endotherm of polymer (a) and polymer with drug (b)

Comparison of DSC endotherms of drug, polymer and polymer with drug showed almost similar peaks which indicated that there was no any interaction between drug and polymer present in the formulation "C".

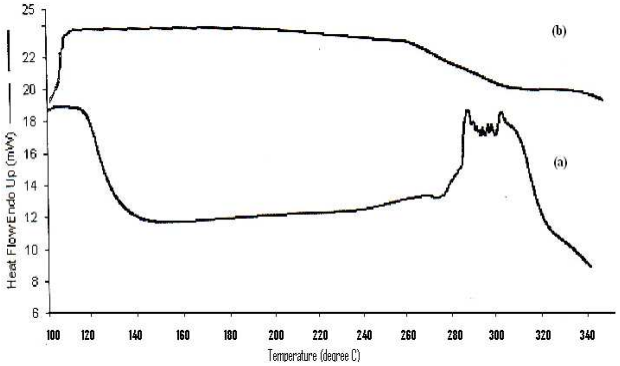


Fig. 11 DSC endotherm of β-Cyclodextrin (a) and drug complexed with β-Cyclodextrin (b)

Comparison of DSC endotherms of β-Cyclodextrin showed some peaks as shown in (Fig. 11a) and when drug was complexed with β-Cyclodextrin as shown in (Fig. 11b), there were no any characteristic peaks of either one, indicated that the drug was completely entrapped within the β-Cyclodextrin molecules and there was no any interaction between drug and β-Cyclodextrin present in the formulation "C-Beta".

CONCLUSION

The gellan gum (Gelrite®) based in situ gelling systems containing ofloxacin, a broad spectrum antibacterial agent used in the treatment of ocular infections and various concentration of Gelrite® for ocular administration have been prepared and evaluated successfully. The gel formed in situ afforded sustained drug release over an 12 hr period. The optimized formulations "C" and "C-Beta" showed satisfactory viscosity, release behavior and antimicrobial quality. Under the conditions 75±5% relative humidity and at 40± 2°C temperature, the dosage forms were stable for a period of 3 months.

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